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10/802,643	03/17/2004	Paul Noel Holvoet	91752CON1	3956

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,643	HOLVOET ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-74* is/are rejected.

7)☒ Claim(s) *56-60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's response to the Office Action mailed January 30, 2006 is acknowledged (paper filed 6/5/06). In the amendment filed therein the specification was modified. Currently claims 56-74 are pending and under consideration.

2. Rejections and/or objections of record not reiterated below have been withdrawn.

OBJECTIONS WITHDRAWN

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the Examiner on form PTO-892 or Applicant on form PTO-1449 has cited the references they have not been considered.

4. The Information Disclosure Statements filed on 3/17/04, 6/18/04, 6/23/04, and 11/10/05 were considered as to the merits prior to First Action.

5. The Information Disclosure Statement filed on 1/5/06 has been considered as to the merits prior to Final Action.

Specification

6. The disclosure is objected to because of the following informalities: Page 1 of the disclosure should be updated to include US Patent #6,727,102. Appropriate correction is required.

The specification has been updated to include US patent #6,727,102. Accordingly the objection is withdrawn.

NEW GROUNDS OF REJECTIONS

Claim Objections

7. Claims 56-60 are objected to because of the following informalities: The claims recite an "antibody with high affinity *contain* at least XXX substituted lysine moieties". It appears that a term is missing from the claim language and should be added for clarification. For example, the claims should recite "the first antibody has high affinity and contains at least XXX substituted lysine moieties", for clarity. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 73 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 73, the use of the term "derived" is indefinite. As recited it is not clear if Applicant intends to mean the sample is found in a human beings body fluid, a sample produced (derived) from a human or is the sample simply "body fluid". Further it is not clear as to what said production(derivation) encompasses. Accordingly, the metes and bounds of the claim cannot be determined. It is suggested that the claims read on human blood samples as exemplified in the disclosure. Please correct.

B. Claim 56 is vague and indefinite because the term "capable" does not positively limit the claim language. It has been held that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138. It is suggested that the term "capable of" be removed from the claim language in order to obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 56-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth monoclonal antibodies mAb-4E6 and mAb-8A2 (see page 6 of the disclosure) and therefore the written description is not commensurate in scope with the claims drawn to any and all antibodies that bind human MDA-modified LDL and OxLDL with high affinity further containing substituted lysine moieties per apo B-100 moiety.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117).

The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of mAb-4E6 and mAb-8A2, the skilled artisan cannot envision the detailed structure of the infinite encompassed possible antibodies reading on the claimed invention and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The monoclonal/polyclonal antibody itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of a compound/seq.id/etc. by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules, usually defined by a sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description ...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

However, no disclosure, beyond the mAb-4E6 and mAb-8A2 is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guildlines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only the isolated antibodies mAb-4E6 and mAb-8A2, but not any and all antibodies that bind human MDA-modified LDL and OxLDL would meet the full breadth of the claims as required by the written description provision of 35 USC 112, first paragraph.

10. Claims 56-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide description of or enablement for any and every antibody population specific for binding human MDA-modified LDL and OxLDL with high affinity and having substituted lysine moieties per apo B-100 moiety, other than antibody mAb-4E6 and mAb-8A2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant provides guidance for the above noted antibodies and provides no guidance as to what modifications or structure are important for the predictable function of any other monospecific antibody. Very different structures may be found on antibodies with the same specificity. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. See reference to Schier et al. (Journal of Molecular Biology, 1996, 263, pages 551-567).

These observations indicate that divergent variable region sequences, both in and out of complementarity's-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Conversely, similar structure may be found on antibodies having different specificities.

In the absence of any guidance other than to the use of mAb-4E6 and mAb-8A2 antibodies, one would not know or be able to predict what structure or modifications were important and the amount of experimentation required to determine the same would be undue. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. As contended by applicant the existence and representation of antibodies with strong inhibitory properties depends on many unpredictable factors. (See page 13 - 1st paragraph of Applicant's response filed 6/5/06). Further, the art indicates that it would require undue experimentation to formulate and use a successful antibody as recited in the instant invention without the prior demonstration of specific limitations that have not been recited. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (18 USPQ 2d 1027 (CAFC 1991)). Accordingly the claims are not commensurate in scope to the invention.

11. Claim 73 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide description of or enablement for any and every body fluid derived from a human being. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant provides guidance for blood sampling to assay for MDA-modified LDL and OxLDL, however no other samples are contemplated or tested in the instant disclosure. Considering the infinite number of possible body fluids derived from human beings (urine, cerebral spinal fluid, sputum, saliva, embryonic fluid, etc), as well as their diverse and distinct characteristics a single blood sample can not read on any and all other fluid samples found in human beings or derived from human beings.

In the absence of any guidance other than to the use of blood sampling, one would not know or be able to predict what structure or modifications were important and the amount of experimentation required to determine the same would be undue. Note that an enabling disclosure for the preparation and use of only a few analogs does not enable all possible analogs where the characteristics of the analogs are unpredictable. Accordingly the claims are not commensurate in scope to the invention.

Double Patenting

12. Double patenting obviousness-type rejection:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 56 and 61-74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-54 of US Patent #6,309,888 as supported by Liu et al. (American Heart Journal, 1992, 123(2), pages 285-290).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are drawn to the detection of human MDA-modified LDL and human OxLDL in a sample.

Claims 1-54 in US Patent #6,309,888 detects multiple markers in the claimed method, however the measurement of additional markers is encompassed by the single marker method recited in claims 56 and 61-74 of the instant application. Further, both methods are drawn to claims that utilizing the same reagents (i.e., mAb-8A2) and measure the same markers (MDA-modified LDL and OxLDL).

The instant claims (56 and 61-74) differ from US Patent #6,309,888 in not specifically teaching the correlation of detected MDA-modified LDL and/or OxLDL to coronary artery disorders. However, limitations reciting the utility of the detected markers in claims 1-54 of US Patent #6,309,888 are not given patentable weight.

The intended use of the method is not germane to the issue of patentability of the method itself. Therefore, these limitations have not been given patentable weight.

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Further, the correlation of the MDA modified-LDL and OxLDL markers to coronary disease was previously known in the prior art. This fact is support by Liu et al.

Liu et al. disclose the involvement of MDA-modified LDL and OxLDL in coronary heart disease patients. MDA-modified LDL was significantly higher in coronary heart disease patients when compared with control subjects. See page 288 and figure 2. Oxidized LDL cholesterol was higher with greater sensitivity in patients with coronary artery disease. See page 289 2nd column and figure 3.

Liu et al. also disclose that their results may have pathological significance and are consistent with a role for oxidative LDL in the coronary disease process in humans. See page 289.

14. Claims 57-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-54 of US Patent #6,309,888 as supported by Liu et al. (American Heart Journal, 1992, 123(2), pages 285-290) in view of Haberland et al. (Proceedings of the National Academy of Science, USA, Vol.79, March 1982, pages 1712-1716).

Please see the discussion of claims 1-54 of US Patent #6,309,888 as supported by Liu et al. set forth above.

Claims 1-54 of US Patent #6,309,888 as supported by Liu et al. differ from the instant invention in not specifically teaching increased substitutions of the lysine moieties per apo B-100 moiety. The substitutions being at least 90, 120, 210, or 240 lysines.

However lysine substitutions of at least 60 out of 356 lysines of the apo B-100 moiety is taught to be useful in the recognition of scavenger receptors. See specification page 2 lines 1-11. This is also taught in the reference of Haberland et al. Harberland et al. teach that the interaction of a minimum of 30 mol of malondialdehyde(MDA)/mol of LDL (60 lysine residues) is required to stimulate the recognition of the scavenger receptor. See page 1716 1st paragraph.

These scavenger receptors promote cholesteryl esterification, are involved in foam cell formation, are responsible for un vivo clearance of modified LDL, and is related to various diseases. See page 1716 1st column. Absent evidence to the contrary the modification of at least 60 lysine residues in the apo B-100 moiety is deemed obvious.

Therefore, One of ordinary skill in the art would have modified at least 60 lysine residues as taught by Haberland et al. in the claims of US Patent #6,309,888 because Haberlabd et al. taught that the interaction of a minimum of 30 mol of malondialdehyde(MDA)/mol of LDL (60 lysine residues) is required to stimulate the recognition of the scavenger receptor. See page 1716 1st paragraph. These scavenger receptors promote cholesteryl esterification, are involved in foam cell formation, are responsible for *in vivo* clearance of modified LDL, and is related to various diseases. See page 1716 1st column.

One of ordinary skill would have been motivated to do this because Haberland et al taught that modification of the lysine residues of human MDA-modified LDL effected recognition and uptake of the compound. See abstract. This uptake is important to the clearance of the modified LDL and may help in the treatment of various diseases. See pages 1715-1716.

Response to Arguments

Applicant contends that a two-way test for obviousness-type double patenting should be used in the instant application. This argument was carefully considered but not found persuasive because, "even if the application at issue is the earlier filed application, only a one-way determination of obviousness is needed to support a double patenting rejection in the absence of a finding *: (A) >of< administrative delay on the part of the Office causing delay in prosecution of the earlier filed application; and (B) >that< applicant could not have filed the conflicting claims in a single (i.e., the earlier filed) application". See MPEP § 804, paragraph II.B.1.(b).

In response to the argument that the obviousness-type double patenting rejection is improper because the one-way test has not been meet, it is noted that the claims in U.S. Patent #6,309,888 are directed to methods that evaluate coronary artery disease via the detection of at least two markers. While the instant claims read on methods for measuring MDA-modified LDL and OxLDL. However, the claims in the instant application are not limited to measurement of MDA-modified LDL and OxLDL because the claims employ the open language "comprising" which reads on the measurement of additional markers (at least two markers). Both sets of claims detect the same markers with the same antibodies. This is evident in claims 2, 3, 9, 14, 16, 18, 20, 21, 24, 27, 29, 30, 36, 41, 42, 45, 46, 48-51, and 53-54 in US Patent #6,309,888, for example. And further, exemplified for example, in claims 56 and 72 of the instantly claimed invention. Both methods utilize monoclonal antibody mAb-8A2 produced by hybridoma Hyb8A2 deposited at the BCCM under deposit accession number LMBP 1661 CB.

Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent>, or a non-commonly owned patent but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3),< when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent. See Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 58 USPQ2d *>1869< (Fed. Cir. 2001); Ex parte Davis, 56 USPQ2d 1434, 1435-36

(Bd. Pat. App. & Inter. 2000). Because both claims are drawn to method of detecting MDA-modified LDL and OxLDL they are not patentably distinct. Although the instant claims do not correlate the detected markers to coronary artery disease, the intended use of the method is not germane to the issue of patentability of the method itself. Therefore, these limitations have not been given patentable weight.

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 56, 61-71, and 73 are rejected under 35 U.S.C. 102(a) as being anticipated by Palinski et al. (Journal of Clinical Investigation, Vol.98, No.3, August 1996, pages 800-814) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430).

Palinski et al. disclose methods for producing antibodies specific for binding LDL. Some E0 antibodies generated for binding to malondialdehyde-LDL(MDA) also bind or recognize copper oxidized LDL. See abstract. The antibodies were utilized to detect LDL levels in plasma. See page 810.

With respect to claims 61-65 and 73, antibody specificity was determined in solid phase competitive solid-phase RIAs. Serum samples were employed and measured against purified monoclonal antibodies (EO1 through EO17) and natural monoclonal antibody of LDL and MDA2. See page 802, for example.

With respect to claim 66, immunohistochemical procedures are taught in figure 6, page 808-809, for example.

With respect to claims 67-71, although Palinski et al. are silent with respect to the binding affinity of the antibodies (Applicant's "high affinity") this limitation is viewed as an inherent property of antibodies.

This is supported by the reference to Winzor et al. wherein it is taught that association constants for specific interactions between ligands and macromolecules can range from 10^3 to 10^{15} M^{-1}. See page 380 and page 381 2nd paragraph. Therefore, binding within this range with "high affinity" necessarily reads on antibody binding interaction.

II. Claims 56, 61-65, 67-71 and 73, is rejected under 35 U.S.C. 102(b) as being anticipated by Kotani et al. (Biochimica et Biophysica Acta, 1215, 1994, pages 121-125) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430).

Kotani et al. disclose methods for detecting MDA-LDL. Antibody ML25 was employed to bind MDA-LDL. However ML25 also bound OxLDL. This antibody was utilized in an ELISA procedure to measure MDA-LDL and OxLDL. See abstract, figure 1, and page 123 Results.

With respect to claim 61, competitive assays are taught in figure 1 and age 122 section 2.4, for example.

With respect to claim 62, MDA-modified LDL is bound to a substrate (solid phase) on page 123 section 3.1.

With respect to claims 63-65, sandwich ELISA procedures are taught on page 124 section 2.5, for example. The assay employs two antibodies (anti-MDA-LDL monoclonal antibody and a monoclonal antibody against apo B –AB16).

With respect to claims 67-71, although, Kotani et al. are silent with respect to the binding affinity of the antibodies (Applicant's "high affinity") this limitation is viewed as an inherent property of antibodies.

This is supported by the reference to Winzor et al. wherein it is taught that association constants for specific interactions between ligands and macromolecules can range from 10^3 to 10^{15} M^{-1}. See page 380 and page 381 2nd paragraph. Therefore, binding within this range with "high affinity" necessarily reads on antibody binding interaction.

With respect to claim 73, serum samples were utilized as specimens. See page 123 section 2.8, for example.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

III. Claims 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palinski et al. (Journal of Clinical Investigation, Vol.98, No.3, August 1996, pages 800-814) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) in view of Haberland et al. (Proceedings of the National Academy of Science, USA, Vol.79, March 1982, pages 1712-1716).

Please see Palinski et al. (Journal of Clinical Investigation, Vol.98, No.3, August 1996, pages 800-814) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) as set forth above.

Palinski et al. (Journal of Clinical Investigation, Vol.98, No.3, August 1996, pages 800-814) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) differ from the instant invention in not specifically teaching increased substitutions of the lysine moieties per apo B-100 moiety. The substitutions being at least 90, 120, 210, or 240 lysines.

However lysine substitutions of at least 60 out of 356 lysines of the apo B-100 moiety is taught to be useful in the recognition of scavenger receptors. See specification page 2 lines 1-11. This is also taught in the reference of Haberland et al. Harberland et al. teach that the interaction of a minimum of 30 mol of malondialdehyde(MDA)/mol of LDL (60 lysine residues) is required to stimulate the recognition of the scavenger receptor. See page 1716 1st paragraph. These scavenger receptors promote cholesteryl esterification, are involved in foam cell formation, are responsible for un vivo clearance of modified LDL, and is related to various diseases. See page 1716 1st column.

Absent evidence to the contrary the modification of at least 60 lysine residues in the apo B-100 moiety is deemed obvious.

Therefore, One of ordinary skill in the art would have modified at least 60 lysine residues as taught by Haberland et al. in the method of Palinski et al. (Journal of Clinical Investigation, Vol.98, No.3, August 1996, pages 800-814) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) because Haberlabd et al. taught that the interaction of a minimum of 30 mol of malondialdehyde(MDA)/mol of LDL (60 lysine residues) is required to stimulate the recognition of the scavenger receptor. See page 1716 1st paragraph. These scavenger receptors promote cholesteryl esterification, are involved in foam cell formation, are responsible for *in vivo* clearance of modified LDL, and is related to various diseases. See page 1716 1st column.

One of ordinary skill would have been motivated to do this because Haberland et al taught that modification of the lysine residues of human MDA-modified LDL effected recognition and uptake of the compound. See abstract. This uptake is important to the clearance of the modified LDL and may help in the treatment of various diseases. See pages 1715-1716.

IV. Claim 74 is rejected under 35 U.S.C. 103(a) as being unpatentable over Palinski et al. (Journal of Clinical Investigation, Vol.98, No.3, August 1996, pages 800-814) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) in view of Kondo, Akira et al. (EPO 0 484 863 A1).

Please see Palinski et al. (Journal of Clinical Investigation, Vol.98, No.3, August 1996, pages 800-814) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) as set forth above.

Palinski et al. (Journal of Clinical Investigation, Vol.98, No.3, August 1996, pages 800-814) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) differ from the instant invention in not teaching the detection of human MDA-modified LDL and human OxLDL detection at 0.02mg/dl in undiluted human plasma.

Kondo et al. teach a monoclonal antibody and a sandwich immunoassay for measuring malondialdehyde-modified LDL. (See Abstract, Page 4, lines 9-32, Example 5). Example 5 teaches a sandwich assay-utilizing antibody 290209 which was generated against and reacted with MDA-modified LDL (Table 1, Page 5, Lines 38-42).

The assays comprise the steps of a) binding the first antibody to the substrate (polystyrene ball) and reacting it with human MDA-modified LDL, b) thoroughly washing, c) contacting the complex with peroxidase-labelled anti-apo B antibody and d) visualizing the MDA-modified LDL by the enzymatic reaction with hydrogen peroxide, orthophenylendiamine as substrates. The second antibody (anti-apo B) has a high affinity to the apo B 100 molecules, which is the predominant apolipoprotein on MDA-modified LDL.

The conditions of the sandwich assay are such that the anti apo B antibody can only react with MDA-modified LDL, as all other LDL of the original sample are washed in step b).

The preparation of the MDA-modified LDL according to the reference of Kondo et al. does not differ significantly from the preparation according to the instant invention.

The sensitivity of the antibodies found in the reference of Kondo et al., in particular No 29210 is at least as high as the sensitivity of antibodies according to the present application.

In particular, antibody 29210 disclosed by Kondo et al., shows a detection limit of less than 0.01 mg/dl MDA modified LDL in an ELISA (Example 4, figure 5). The antibody of the present application is capable of detecting 0.02 mg/dl of MDA-modified LDL in a competitive ELISA (disclosure page 17, lines 1-2).

Therefore, One of ordinary skill in the art would produce and utilize various comparative antibody constructs directed to different detection limits such as 0.02mg.dl as taught by Kondo et al. in the method of Palinski et al. as evidenced by Winzor et al. because Kondo et al. teach antibodies meeting the claimed detection limits. Such modifications for the resulting data sets to evaluated and detect different limits are routine performed and are almost always determined and used in optimizing immunoassay studies. Unless the result obtained in the instant application is a significant and unexpected difference over the prior art, it would have been prima facie obvious for one of ordinary skill in the art to vary the detection limits in the given parameters to determine the unknown as a means of optimizing the assays provided by the art.

One of ordinary skill would have been motivated to do maximize the detection capabilities of the assays taught by the prior art.

V. Claims 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kotani et al. (Biochimica et Biophysica Acta, 1215, 1994, pages 121-125) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) in view of Haberland et al. (Proceedings of the National Academy of Science, USA, Vol.79, March 1982, pages 1712-1716).

Please see Kotani et al. (Biochimica et Biophysica Acta, 1215, 1994, pages 121-125) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) as set forth above.

Kotani et al. (Biochimica et Biophysica Acta, 1215, 1994, pages 121-125) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) differ from the instant invention in not specifically teaching increased substitutions of the lysine moieties per apo B-100 moiety. The substitutions being at least 90, 120, 210, or 240 lysines.

However lysine substitutions of at least 60 out of 356 lysines of the apo B-100 moiety is taught to be useful in the recognition of scavenger receptors. See specification page 2 lines 1-11. This is also taught in the reference of Haberland et al. Harberland et al. teach that the interaction of a minimum of 30 mol of malondialdehyde(MDA)/mol of LDL (60 lysine residues) is required to stimulate the recognition of the scavenger receptor. See page 1716 1st paragraph. These scavenger receptors promote cholesteryl esterification, are involved in foam cell formation, are responsible for un vivo clearance of modified LDL, and is related to various diseases. See page 1716 1st column. Absent evidence to the contrary the modification of at least 60 lysine residues in the apo B-100 moiety is deemed obvious.

Therefore, One of ordinary skill in the art would have modified at least 60 lysine residues as taught by Haberland et al. in the method of Kotani et al. (Biochimica et Biophysica Acta, 1215, 1994, pages 121-125) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) because Haberlabd et al. taught that the interaction of a minimum of 30 mol of malondialdehyde(MDA)/mol of LDL (60 lysine residues) is required to stimulate the recognition of the scavenger receptor. See page 1716 1st paragraph.

These scavenger receptors promote cholesteryl esterification, are involved in foam cell formation, are responsible for *in vivo* clearance of modified LDL, and is related to various diseases. See page 1716 1st column.

One of ordinary skill would have been motivated to do this because Haberland et al taught that modification of the lysine residues of human MDA-modified LDL effected recognition and uptake of the compound. See abstract. This uptake is important to the clearance of the modified LDL and may help in the treatment of various diseases. See pages 1715-1716.

VI. Claim 74 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kotani et al. (Biochimica et Biophysica Acta, 1215, 1994, pages 121-125) as evidenced by Winzor et al. (Journal of Chromatography, 492, 1989, pages 377-430) in view of Kondo, Akira et al. (EPO 0 484 863 A1).

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The preparation of the MDA-modified LDL according to the reference of Kondo et al. does not differ significantly from the preparation according to the instant invention. The sensitivity of the antibodies found in the reference of Kondo et al., in particular No 29210 is at least as high as the sensitivity of antibodies according to the present application.

In particular, antibody 29210 disclosed by Kondo et al., shows a detection limit of less than 0.01 mg/dl MDA modified LDL in an ELISA (Example 4, figure 5). The antibody of the present application is capable of detecting 0.02 mg/dl of MDA-modified LDL in a competitive ELISA (disclosure page 17, lines 1-2).

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One of ordinary skill would have been motivated to do maximize the detection capabilities of the assays taught by the prior art.

Response to Arguments

Applicant's arguments have been carefully considered and were considered above.

Applicants arguments against the cited prior art if record in the Office Action mailed 1/30/06 are MOOT because new grounds of rejection have been set forth.

With respect to EP 0 484 863 A1, applicant contends that the reference does not teach detections limits of 0.02miligrams/deciliter and directs examiner to figure 6. This argument was carefully considered but not found persuasive because figure 5 exemplifies measurements reading on the claimed limitation. Specifically, the lowest detection limit is .001 micrograms/ml to 10 micrograms/ml and this reads on applicants 0.2micrograms/ml (conversion of 0.02milligrams/deciliter) as argued on page 17 of the response filed 6/5/06.

17. For reasons aforementioned, no claims are allowed.

Remarks

18. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Griffin et al. (Diabetic Medicine, 1997, 14, 741-747) teach antibodies that recognize MDA-LDL and OxLDL.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

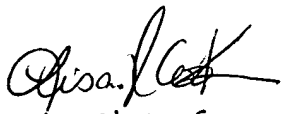
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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